IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
SHIMIZU et al. :
Serial No. 09/800,839 : Group Art Unit 1615
Filed on March 7, 2001 : Examiner TRAN, Susan T
For RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of Patent and Trademarks, Washington, D.C.

Sir,

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd. (now, Takeda Pharmaceutical Company Limited), Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Production Division of said company;

That I have been appointed a Research Head of Pharmaceutical Technology Research & Development Laboratories in said Pharmaceutical Production Division since 2004;

That I am a member of the Pharmaceutical Society of Japan, and have published, with other research workers, a number of reports on scientific studies, among others, including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)
2. Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1029-1035 (2003)
3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003) ;

That I am one of the co-inventors of the United States Patent Application Serial No. 09/800,839 filed on March 7, 2001;

That the following Experiment was conducted by myself and under my supervision and control:

Study on Oral disintegrability of Effervescent Preparations by Lundberg *et al.*

PURPOSE

The oral disintegrability of effervescent preparations of U.S. Patent No. 6,132,770 (Lundberg *et al.*) have been evaluated and then have been examined whether this patent could be directed to an invention for the use as an orally disintegrating tablet.

PROCEDURES

The oral disintegrability of the effervescent preparations of Lundberg *et al.* have been evaluated by using the preparation procedures and the combination ratios as set forth in Example 3 of Lundberg *et al.*, except omeprazole was replaced with lansoprazole. Comparisons between Example 3 of Lundberg *et al.* and this formulation, and the preparation methods thereof are shown.

1. Preparation of Enteric-coated Granules

1.1 Active Compound Layer

Table 1 Formulation of Core and Active Compound Layer

Material	Example 3	Studied Product
Non-pareil core	10.0 kg(63.3%)	750 g(63.3%)
Magnesium omeprazole	5.0 kg(31.6%)	-
Lansoprazole	-	375 g(31.6%)
Hydroxypropyl methylcellulose	0.8 kg(5.1%)	60 g(5.1%)
Purified water	14.3 kg	1072.5 g
Total	15.8 kg	1185.0 g

Lansoprazole and hydroxypropyl methylcellulose were dissolved and suspended in purified water. Using a Wurster equipped fluidized-bed granulator, the non-pareil core was spray-coated with the suspension and was dried.

1.2. Intermediate Layer

Table 2 Formulation of Intermediate Layer

Material	Example 3	Studied Product
Core material with active compound layer	14.6 kg(77.7%)	1095.0 g(77.7%)
Hydroxypropyl cellulose	1.5 kg(8.0%)	112.5 g(8.0%)
Talc	2.5 kg(13.3%)	187.5 g(13.3%)
Magensium Stearate	0.2 kg(1.0%)	15 g(1.0%)
Purified water	29.2 kg	2190.0 g
Total	18.8 kg	1410.0 g

Hydroxypropyl cellulose, talc and magnesium stearate were dissolved and suspended in purified water. Using a Wurster equipped fluidized-bed granulator, the core material with the active compound layer was spray-coated with the suspension and was dried.

1.3. Enteric Layer

Table 3 Formulation of Enteric Layer

Material	Example 3	Studied Product
Active granules	250 g(54.9%)	500.0 g(54.9%)
Methacrylic acid copolymer(30% suspension)	458 g(30.2%)	916.0 g(30.2%)
Triethyl citrate	41 g(9.0%)	82.0 g(9.0%)
Titanium dioxide	19 g(4.2%)	38.0 g(4.2%)
Mono- and diglycerides	7 g(1.5%)	14.0 g(1.5%)
Polysorbate 80	0.7 g(0.2%)	1.4 g(0.2%)
Purified water	329 kg	658.0 g
Total	455.1 g	910.2 g

A methacrylic acid copolymer (30% suspension) was adjusted to pH of 4.0 with a 0.5 M aqueous sodium hydroxide solution. Thereafter all of the triethyl citrate was added. (Suspension A).
Polysorbate 80 was dissolved in a portion of purified water and was heated to 70°C, to which was added mono- and diglycerides. The mixture was dispersed with a disperser and then cooled to room temperature (Emulsion B). Thereafter, titanium dioxide was added and dispersed to a portion of purified water (Suspension C). Emulsion B, Suspension C and the remaining purified water were portionwise added to Suspension A. Using a Wurster equipped fluidized-bed granulator, the active granules were spray-coated with the suspension and dried.

2. Effervescent Granules

Table 4 Formulation of Effervescent Granules

Material	Example 3	Studied Product
Citric acid anhydrous	11.4 kg(56.7%)	570.0 g(56.7%)
Sodium bicarbonate	8.4 kg(41.8%)	420.0 g(41.8%)
Polyvinylpyrrolidone K-25	0.3kg(1.5%)	15.0 g(1.5%)
EtOH 99%(w/v)	0.8 kg	40.0 g
Purified water	0.3 kg	15.0 g
Total	20.1 kg	1060.0 g

Polyvinylpyrrolidone K-25 was dissolved in a mixed solution of ethanol and purified water. Citric acid anhydrous and sodium bicarbonate were mixed by using a

mortar, which was then added and compounded to the mixed solution. Then, the mixture was dried at 55°C using a lathe dryer and was granulated using 1000 μm of a standard sieve.

3. Pre-mix of Sodium Carbonate

Table 5 Formulation of Effervescent Granules

Material	Example 3	Studied Product
Sodium carbonate anhydrous	38 g(18.6%)	76.0 g(18.6%)
Sorbitol	160 g(78.5%)	320.0 g(78.5%)
Antifoam M	5.8 g(2.9%)	11.6 g(2.9%)
Total	203.8 g	407.6 g

Using a mortar, sodium carbonate anhydrous, sorbitol and an antifoam M were mixed.

4. Mixed Granules and Tablets

Table 6 Formulation of Mixed Granules

Material	Example 3	Studied Product
Effervescent granules	909 g(76.4%)	909.0 g(76.4%)
Pre-mix	204 g(17.1%)	204.0 g(17.1%)
Sodium sterylfumarate	7 g(0.6%)	7.0 g(0.6%)
Enteric coated microgranules	70 g(5.9%)	70.0 g(5.9%)
Total	1190 g	1190.0 g

Effervescent granules, the pre-mix, sodium sterylfumarate and the enteric coated microgranules were mixed and put into 50 bags. 2970m g of the mixed granules were weighed, and made into tablets using a universal testing machine UH-10A (Shimadzu) and using a flat pestle having an angle of 25 mmϕ under a tableting pressure of 20 KN/punch.

5. Characteristics of Tablets

Thickness, hardness and friability of the orally disintegrating tablets were measured.

Thickness: Thickness of 4 tablets were measured using a Dialgauge and were averaged.

Hardness: Hardness of 10 tablets were measured using a hardness tester (Toyama Company) and were averaged.

Oral Disintegration Time: Three individuals participated in this test. The participants brushed their teeth before the test and then took one tablet without swallowing the tablet. Thereafter, the disintegration time of the tablet was measured.

RESULTS

The results of the measurements are shown in Table 7, as it can be seen the thickness and hardness equivalent to those in Example 3 were obtained. For the oral disintegrability, it was hard to retain the tablet in the mouth due to the generation of carbonic acids, and thus the individuals vomited the tablet after 3 minutes. Even in such a case, it was shown that the tablet did not disintegrate even approximately by half. Thus, it was determined that the effervescent granules had difficulty of being applied as an orally disintegrating tablet.

Table 7 Results of Measurements

	Example 3 (Values as described in Lundberg *et al.*)	Studied Product
Thickness (Average)	4.3 mm	4.29 mm
Hardness (Average)	77 N	77.9 N
Oral Disintegration Time		Not disintegrated for 3 minutes Not tolerated due to the generation of carbonic acids, which caused the tablet to be vomited.

CONCLUSION

As described in European Pharmacopoeia, effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates which react in the presence of water to release carbon dioxide. They are intended to be dissolved and dispersed in water before administration. On the other hand, orodispersible tablets (orally disintegrating tablets) are uncoated tablets intended to be placed in the mouth where they can disperse rapidly before being swallowed. Effervescent tablets and orally disintegrating tablets have different uses for taking a medicine. Therefore, we strongly believe that technologies for effervescent tablets don't apply to the design of orally disintegrating tablets.

The purpose of this study was to determine the possibility of application of technologies for effervescent tablets to the design of orally disintegrating tablets. The effervescent tablets of U.S. Patent No. 6,132,770 (Lundberg et al.) didn't disintegrate in the mouth within 3 minutes.

Therefore the above-described experiments confirm that technologies for effervescent tablets don't apply to the design of orally disintegrating tablets.

It is declared by the undersigned that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 18 th day of January, 2005.

Toshihiro Shimizu

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